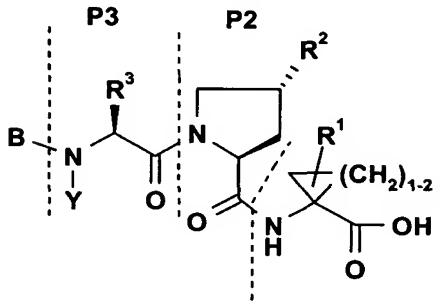
CLAIMS

We Claim:

1. A pharmaceutical composition comprising:

(a) a compound having the following formula (I):



(I)

wherein **B** is H, a C_6 or C_{10} aryl, C_{7-16} aralkyl; Het or (lower alkyl)-Het, all of which optionally substituted with C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyl; hydroxy; hydroxyalkyl; halo; haloalkyl; nitro; cyano; cyanoalkyl; amino optionally substituted with C_{1-6} alkyl; amido; or (lower alkyl)amide;

or **B** is an acyl derivative of formula $\mathbf{R_4}$-C(O)-; a carboxyl derivative formula $\mathbf{R_4}$-O-C(O)-; an amide derivative of formula $\mathbf{R_4}$-N($\mathbf{R_5}$)-C(O)-; a thioamide derivative of formula $\mathbf{R_4}$-N($\mathbf{R_5}$)-C(S)-;or a sulfonyl derivative of formula $\mathbf{R_4}$-SO_2 wherein

$\mathbf{R_4}$ is (i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido, or (lower alkyl) amide;

(ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalkyl, all optionally substituted with hydroxy, carboxyl, (C_{1-6} alkoxy)carbonyl, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido, or (lower alkyl) amide;

(iii) amino optionally mono- or di-substituted with C_{1-6} alkyl; amido; or (lower alkyl)amide;

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted

with C_{1-6} alkyl; or

(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl) amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

$\mathbf{R_5}$ is H or C_{1-6} alkyl;

with the proviso that when **B** is a carboxyl derivative, an amide derivative or a thioamide derivative, $\mathbf{R_4}$ is not a cycloalkoxy;

Y is H or C_{1-6} alkyl;

$\mathbf{R^3}$ is C_{1-8} alkyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, all optionally substituted with hydroxy, C_{1-6} alkoxy, C_{1-6} thioalkyl, amido, (lower alkyl)amido, C_6 or C_{10} aryl, or C_{7-16} aralkyl;

$\mathbf{R^2}$ is CH_2-$\mathbf{R_{20}}$, NH-$\mathbf{R_{20}}$, O-$\mathbf{R_{20}}$ or S-$\mathbf{R_{20}}$, wherein $\mathbf{R_{20}}$ is quinolyl or (lower alkyl)quinolyl, both optionally mono-, di- or tri-substituted with $\mathbf{R_{21}}$,

wherein each $\mathbf{R_{21}}$ is independently C_{1-6} alkyl; C_{1-6} alkoxy; lower thioalkyl; sulfonyl; NO_2; OH; SH; halo; haloalkyl; amino optionally mono- or di-substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-14} aralkyl, Het or (lower alkyl)-Het; amido optionally mono-substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-14} aralkyl, Het or (lower alkyl)-Het; carboxyl; carboxy(lower alkyl); C_6 or C_{10} aryl, C_{7-14} aralkyl or Het, said aryl, aralkyl or Het being optionally substituted with $\mathbf{R_{22}}$;

wherein $\mathbf{R_{22}}$ is C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{1-6} alkoxy; amino optionally mono- or di-substituted with C_{1-6} alkyl or C_{3-7}cycloalkyl; sulfonyl; (lower alkyl)sulfonyl; NO_2; OH; SH; halo; haloalkyl; carboxyl; amide; (lower alkyl)amide; or Het optionally substituted with C_{1-6} alkyl;

$\mathbf{R^1}$ is H; C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, all optionally substituted with halogen;

or a tautomer thereof.

(b) about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a mixture of pharmaceutically acceptable amines; and

(c) one or more pharmaceutically acceptable oils, carriers or hydrophilic solvents;

and when (c) is one or more pharmaceutically acceptable oils, the pharmaceutical composition further comprises:

(d) optionally one or more pharmaceutically acceptable hydrophilic solvents;

(e) optionally one or more pharmaceutically acceptable polymers;

and

(f) optionally one or more pharmaceutically acceptable surfactants;

and when (c) is one or more pharmaceutically acceptable carriers, the pharmaceutical composition further comprises:

(d) optionally one or more pharmaceutically acceptable surfactants.

2. A pharmaceutical composition according to claim 1, wherein the compound of formula (I) is present in an amount of from about 1% to 50% by weight.

3. A pharmaceutical composition according to claim 1, wherein the amine is present in an amount of from about 0.1% to 7% by weight.

4. A pharmaceutical composition according to claim 1, wherein the amine is a C_{1-6} alkylamine, di-(C_{1-6} alkyl)-amine or tri-(C_{1-6} alkyl)-amine, wherein one or more alkyl groups thereof may be optionally substituted by one or more hydroxy groups, or the amine is C_{1-6} alkylenediamine, a basic amino acid or choline hydroxide, or mixtures thereof.

5. A pharmaceutical composition according to to claim 1, wherein the amine is selected from ethanolamine, diethanolamine, triethanolamine, tris(hydroxymethyl)aminomethane, ethylenediamine or dimethylaminoethanol, or mixtures thereof.

6. A pharmaceutical composition according to to claim 1, wherein the one or more pharmaceutically acceptable oils, carriers or hydrophilic solvents are present in an

amount of from about 1% to 99% by weight.

7. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable oil is selected from: medium or long chain mono-, di- or triglycerides, water insoluble vitamins, fatty acids and mixtures thereof.

8. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable oil is selected from: mono-, di- or triglycerides of caprylic fatty acids; mono-, di- or triglycerides of capric fatty acids; oleic acid, and mixtures thereof.

9. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable carrier is selected from a pharmaceutically acceptable polymer and a pharmaceutically acceptable urea.

10. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable carrier is selected from polyethylene glycols, polyvinylpyrrolidones, polyvinylalcohols, cellulose derivatives, polyacrylates, polymethacrylates, polyglycolyzed glycerides, ureas, sugars, polyols, and mixtures thereof.

11. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable hydrophilic solvent is selected from propylene glycol, polypropylene glycol, polyethylene glycol, glycerol, ethanol, dimethyl isosorbide, glycofurol, propylene carbonate, dimethyl acetamide, water, or mixtures thereof.

12. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable hydrophilic solvent is selected from propylene glycol,

polyethylene glycol, ethanol, water, and mixtures thereof.

13. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable polymer is present in an amount of up to about 50% by weight.

14. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable polymer is selected from polyethylene glycols, polyvinylpyrrolidones, polyvinylalcohols, cellulose derivatives, polyacrylates, polymethacrylates, sugars, polyols, and mixtures thereof.

15. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable surfactant is present in an amount of up to about 70% by weight.

16. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable surfactant is selected from d-alpha tocopheryl polyethylene glycol 1000 succinate, polyoxyl castor oils, polysorbates, peglicol 6-oleate, polyoxyethylene stearates, polyglycolyzed glycerides or poloxamers, or sodium lauryl sulfate and mixtures thereof.

17. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable surfactant is selected from d-alpha tocopheryl polyethylene glycol 1000 succinate, polyoxyl 40 hydrogenated castor oil, polyoxyl 35 castor oil, polyoxypropylene-polyoxyethylene block copolymer, or sodium lauryl sulfate, and mixtures thereof.

18. A pharmaceutical composition according to claim 1, further comprising one or more pharmaceutically acceptable bases.

19. A pharmaceutical composition according to claim 18, wherein the

pharmaceutically acceptable bases is selected from sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, magnesium hydroxide, and magnesium aluminum hydroxide.

20. A pharmaceutical composition according to claim 1, wherein in the compound of formula (I):

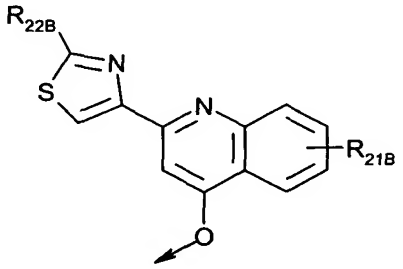
B is a carboxyl derivative of formula $\mathbf{R_4}$-O-C(O)-, wherein $\mathbf{R_4}$ is

C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

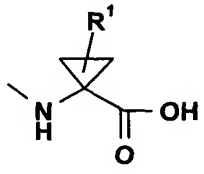
Y is H or methyl;

$\mathbf{R^3}$ is C_{1-8} alkyl;

$\mathbf{R^2}$ is:



wherein $\mathbf{R_{22B}}$ is C_{1-6} alkyl; amino optionally mono- or di-substituted with C_{1-6}alkyl or C_{3-7} cycloalkyl; (lower alkyl)amide; or amido; and $\mathbf{R_{21B}}$ is C_{1-6} alkyl, C_{1-6} alkoxy, amino, di(lower alkyl)amino, (lower alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl; and

P1 is 

and $\mathbf{R^1}$ is ethyl, vinyl, cyclopropyl, 1 or 2-bromoethyl or 1 or 2-bromovinyl.

21. A pharmaceutical composition according to claim 1, comprising:

(a) a compound of formula (I);

(b) about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a mixture of pharmaceutically acceptable amines; and

(c) one or more pharmaceutically acceptable hydrophilic solvents.

22. A pharmaceutical composition according to claim 1, comprising:

(a) about 5% to 30% by weight of a compound of formula (I);

(b) about 0.5% to 7% by weight of a pharmaceutically acceptable amine; and

(c) about 40% to 99% by weight of pharmaceutically acceptable hydrophilic solvent.

23. A pharmaceutical composition according to claim 1, comprising:

(a) about 5% to 15% by weight of a compound of formula (I);

(b) about 0.5% to 5% by weight of a pharmaceutically acceptable amine; and

(c) about 80% to 99% by weight of pharmaceutically acceptable hydrophilic solvent.

24. A pharmaceutical composition according to claim 1, comprising:

(a) about 5% to 15% by weight of a compound of formula (I);

(b) about 0.5% to 5% by weight of tris(hydroxymethyl)aminomethane; and

(c) about 80% to 90% by weight of a mixture of propylene glycol, ethanol and water.

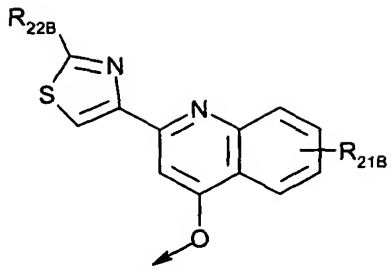
25. A pharmaceutical composition according to claim 24, wherein in the compound of formula (I):

B is a carboxyl derivative of formula $\mathbf{R_4}$-O-C(O)-, wherein $\mathbf{R_4}$ is C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

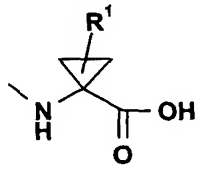
Y is H or methyl;

$\mathbf{R^3}$ is C_{1-8} alkyl;

$\mathbf{R^2}$ is:



wherein $\mathbf{R_{22B}}$ is C_{1-6} alkyl; amino optionally mono- or di-substituted with C_{1-6}alkyl or C_{3-7} cycloalkyl; (lower alkyl)amide; or amido; and $\mathbf{R_{21B}}$ is C_{1-6} alkyl, C_{1-6} alkoxy, amino, di(lower alkyl)amino, (lower alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl; and

P1 is 

and $\mathbf{R^1}$ is ethyl, vinyl, cyclopropyl, 1 or 2-bromoethyl or 1 or 2-bromovinyl.

26. A pharmaceutical composition according to claim 1, comprising:
    (a) a compound of formula (I);
    (b) about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a mixture of pharmaceutically acceptable amines;
    (c) one or more pharmaceutically acceptable oils;
    (d) optionally one or more pharmaceutically acceptable hydrophilic solvents;
    (e) optionally one or more pharmaceutically acceptable polymers; and
    (f) optionally one or more pharmaceutically acceptable surfactants.

27. A pharmaceutical composition according to claim 1, comprising:
    (a) about 5% to 30% by weight of a compound of formula (I);
    (b) about 0.1% to 7% by weight of a pharmaceutically acceptable amine;
    (c) about 1% to 99% by weight of a pharmaceutically acceptable oil;
    (d) up to about 70% by weight of a pharmaceutically acceptable hydrophilic solvent;

(e) optionally up to about 50% by weight of a pharmaceutically acceptable polymer;

(f) up to about 70% by weight of a pharmaceutically acceptable surfactant; and

(g) optionally about 0.1 to 10% by weight of a pharmaceutically acceptable base.

28. A pharmaceutical composition according to claim 1, comprising:

(a) about 10% to 20% by weight of a compound of formula (I);

(b) about 0.1% to 5% by weight of a pharmaceutically acceptable amine;

(c) about 20% to 70% by weight of a pharmaceutically acceptable oil;

(d) about 10% to 30% by weight of a pharmaceutically acceptable hydrophilic solvent;

(e) optionally about 1% to 20% by weight of a pharmaceutically acceptable polymer;

(f) about 20% to 50% by weight of a pharmaceutically acceptable surfactant; and

(g) optionally about 0.1 to 5% by weight of a pharmaceutically acceptable base.

29. A pharmaceutical composition according to claim 1, comprising:

(a) about 10% to 20% by weight of a compound of formula (I);

(b) about 0.1% to 5% by weight of tris(hydroxymethyl)aminomethane;

(c) about 20% to 70% by weight of a mono- or diglyceride of caprylic fatty acid or a mono- or diglyceride of capric fatty acid, or mixtures thereof;

(d) about 10% to 30% by weight of a mixture of propylene glycol, ethanol and optionally water;

(e) optionally about 1% to 20% by weight of polyethylene glycol or polyvinylpyrrolidone; and

(f) about 20% to 50% by weight of d-alpha tocopheryl polyethylene glycol

1000 succinate or polyoxyl 35 castor oil.

30. A pharmaceutical composition according to claim 29, wherein in the compound of formula (I):

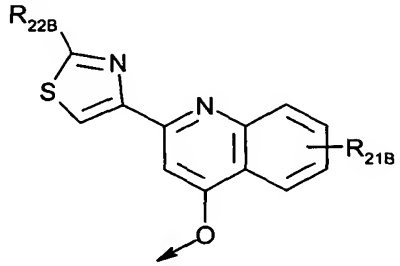
B is a carboxyl derivative of formula $\mathbf{R_4}$-O-C(O)-, wherein $\mathbf{R_4}$ is

C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

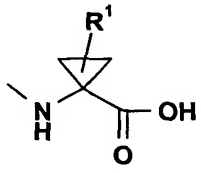
Y is H or methyl;

$\mathbf{R^3}$ is C_{1-8} alkyl;

$\mathbf{R^2}$ is:



wherein $\mathbf{R_{22B}}$ is C_{1-6} alkyl; amino optionally mono- or di-substituted with C_{1-6}alkyl or C_{3-7} cycloalkyl; (lower alkyl)amide; or amido; and $\mathbf{R_{21B}}$ is C_{1-6} alkyl, C_{1-6} alkoxy, amino, di(lower alkyl)amino, (lower alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl; and

P1 is 

and $\mathbf{R^1}$ is ethyl, vinyl, cyclopropyl, 1 or 2-bromoethyl or 1 or 2-bromovinyl.

31. A pharmaceutical composition according to claim 29, said composition further comprising about 0.1 to 5% by weight of sodium hydroxide.

32. A pharmaceutical composition according to claim 1, comprising:

(a) a compound of formula (I);

(b) about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a mixture of pharmaceutically acceptable amines;

(c) one or more pharmaceutically acceptable carriers; and

(d) optionally one or more pharmaceutically acceptable surfactants.

33. A pharmaceutical composition according to claim 1, comprising:

(a) about 5% to 30% by weight of a compound of formula (I);

(b) about 0.1% to 7% by weight of a pharmaceutically acceptable amine;

(c) about 1% to 99% by weight of a pharmaceutically acceptable carrier; and

(d) up to about 50% by weight of a pharmaceutically acceptable surfactant.

34. A pharmaceutical composition according to claim 1, comprising:

(a) about 10% to 20% by weight of a compound of formula (I);

(b) about 0.1% to 5% by weight of a pharmaceutically acceptable amine;

(c) about 60% to 80% by weight of a pharmaceutically acceptable carrier; and

(d) about 1% to 20% by weight of a pharmaceutically acceptable surfactant.

35. A pharmaceutical composition according to claim 1, comprising:

(a) about 10% to 20% by weight of a compound of formula (I);

(b) about 0.1% to 5% by weight of tris(hydroxymethyl)aminomethane;

(c) about 60% to 80% by weight of polyethylene glycol, polyvinylpyrrolidone, lactose or a mixture thereof; and

(d) about 1% to 20% by weight of d-alpha tocopheryl polyethylene glycol 1000 succinate, polyoxypropylene-polyoxyethylene block copolymer or sodium lauryl sulfate.

36. A pharmaceutical composition according to claim 35, wherein in the compound of formula (I):

B is a carboxyl derivative of formula $\mathbf{R_4}$-O-C(O)-, wherein $\mathbf{R_4}$ is

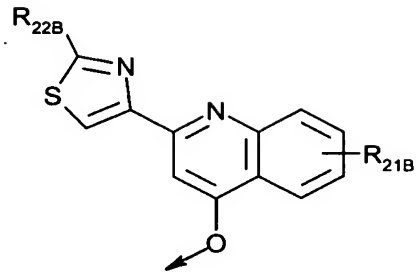
C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, all optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl, amido, (lower alkyl)amide, or amino optionally mono- or

di-substituted with C_{1-6} alkyl;

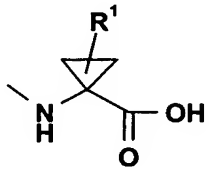
Y is H or methyl;

$\mathbf{R^3}$ is C_{1-8} alkyl;

$\mathbf{R^2}$ is:



wherein $\mathbf{R_{22B}}$ is C_{1-6} alkyl; amino optionally mono- or di-substituted with C_{1-6}alkyl or C_{3-7} cycloalkyl; (lower alkyl)amide; or amido; and $\mathbf{R_{21B}}$ is C_{1-6} alkyl, C_{1-6} alkoxy, amino, di(lower alkyl)amino, (lower alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl; and

P1 is 

and $\mathbf{R^1}$ is ethyl, vinyl, cyclopropyl, 1 or 2-bromoethyl or 1 or 2-bromovinyl;

37. A pharmaceutical composition according to claim 1, in the form of a fluid dosage form selected from a hard shell or softgel capsule or in the form of a solid dosage form selected from a powder, a tablet or a capsule.

38. A pharmaceutical composition according to claim 1, further comprising one or more antioxidants.

39. A pharmaceutical composition according to claim 38, wherein the antioxidant is present in an amount of about 0.01 to 1% by weight.

40. A pharmaceutical composition according to claim 38, wherein the antioxidant is

selected from ascorbic acid, sulfatide salts, citric acid, propyl gallate, dl-α-tocopherol, ascorbyl palmitate, BHT or BHA.

41. A method of manufacturing a pharmaceutical composition according to claim 1, said method comprising:

(A) (a) dissolving the amine(s) in the one or more pharmaceutically acceptable solvents; (b) adding the compound of formula (I) to the solution obtained in step (a) and mixing; or

(B) (a) mixing together the pharmaceutically acceptable oil(s), surfactant(s) and solvent(s); (b) dissolving the pharmaceutically acceptable amine(s) in the mixture obtained in step (a); (c) optionally heating the mixture obtained in step (b) if necessary to sufficiently melt one or more of the components of the mixture; (d) adding the compound of formula (I) to the mixture obtained in steps (b) or (c) and mixing; or

(C) (a) dissolving the pharmaceutically acceptable amine(s), the pharmaceutically acceptable carrier(s) and optionally the pharmaceutically acceptable surfactant(s) in a suitable hydrophilic solvent; (b) adding the compound of formula (I) to the solution obtained in step (a) and mixing to dissolve the compound of formula (I); (c) evaporating the hydrophilic solvent to cause co-precipitation of the compound of formula (I), the amine(s), the carrier(s) and the optional surfactant(s); or

(D) (a) mixing the pharmaceutically acceptable carrier(s) and the optional surfactant(s) and heating the resulting mixture to sufficiently melt the carrier(s) and surfactant(s); (b) adding the pharmaceutically acceptable amine(s) and the compound of formula (I) to the mixture obtained in step (a) and mixing; or

(E) (a) mixing the compound of formula (I), the pharmaceutically acceptable amine(s), the pharmaceutically acceptable carrier(s) and optionally the pharmaceutically acceptable surfactant(s) to form a blend, and (b) optionally adding a lubricant to the blend; or

(F) (a) mixing the compound of formula (I), the pharmaceutically acceptable amine(s), the pharmaceutically acceptable carrier(s) and optionally the pharmaceutically acceptable surfactant(s) while adding water or another

hydrophilic solvent(s) to the mixture to obtain a paste; (b) drying the paste of step (a) to a sufficient level of dryness; and (c) passing the dried paste through a screen.

42. A method of inhibiting the replication of hepatitis C virus by exposing the virus to a hepatitis C viral NS3 protease inhibiting amount of the composition according to claim 1.

43. A method of treating a hepatitis C viral infection in a mammal comprising administering to a mammal in need thereof a therapeutically effective amount of the composition according to claim 1.